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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/050,611	01/16/2002	Darrell H. Carney	3033.1000-008	6599

21005 7590 03/05/2004

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EXAMINER	
WAX, ROBERT A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/050,611	CARNEY, DARRELL H.	
	Examiner	Art Unit	
	Robert A. Wax	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-28 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-28 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *various (5)*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statements filed May 23, 2002, July 26, 2002, November 6, 2002, June 24, 2003 and January 12, 2004 have been considered. Please see the attached initialed PTO-1449s.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. This is the first of two enablement rejections.

Claims 1, 6, 9-19, 24, 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods wherein the angiogenic thrombin derivative peptide is a peptide with angiogenic activity having at least 23 amino acids but not more than 307 amino acids comprising a polypeptide derivative of thrombin which has a thrombin receptor binding domain with a serine esterase conserved sequence, does not reasonably provide enablement for all angiogenic thrombin derivative peptides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the invention commensurate in scope with these claims. The term "angiogenic thrombin derivative" is defined in Carney, US Patent 5,352,664 at column 6, lines 47-53 where it states, "[F]or purposes of the present invention, a thrombin derivative is defined as any molecule with an amino acid sequence derived at least in part from that of thrombin, whether synthesized in vivo or in vitro. Accordingly, a thrombin derivative, as referred to herein, designates a polypeptide molecule which comprises fewer amino acids than thrombin." Thus, within this definition is literally any peptide with angiogenic activity that has fewer amino acids than thrombin, or less than 308 amino acids.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state

of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant case, the amount of experimentation is enormous since the number of peptides having lengths less than 308 amino acids is large, one of skill in the art would have to make and test each one to determine if it had angiogenic activity. The amount of guidance presented is limited to angiogenic thrombin derivative peptides having both a thrombin receptor binding domain and a serine esterase conserved sequence. No discussion is present as to what other motifs or domains might be present. Working examples are presented, however, they show only TP508. The nature of the invention is a new use for known peptides; the state of the prior art is that these thrombin derivatives are known. The ordinary level of skill in this art is very high. The level of predictability of the effect of administering an angiogenic thrombin derivative peptide that is a peptide with angiogenic activity having at least 23 amino acids but not more than 307 amino acids comprising a polypeptide derivative of thrombin which has a thrombin receptor binding domain with a serine esterase conserved sequence is relatively high but the predictability of the effect of administering just any peptide that is shorter than 308 amino acids is as low as it is possible to be. Finally, these claims are very broad in the sense that many millions of different proteins fall within the scope of the claims.

Based on this analysis, the finding of undue experimentation is mandated.

4. This is the second of two enablement rejections.

Claims 1, 6, 9-19, 24, 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for physiologically functional equivalents such as carboxy-terminal amides, amino-terminal acetylates or peptides conjugated to inert substrates, does not reasonably provide enablement for physiologically functional equivalents such as conservative amino acid modifications and substitutions or nonconservative modifications or other undefined "equivalents". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The term "physiologically functional equivalent of a thrombin derivative" is defined in Carney, US Patent 5,352,664 at column 6, lines 54-65 where it states, "A physiologically functional equivalent of a thrombin derivative encompasses molecules which differ from thrombin derivatives in particulars which do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence. Such particulars may include, but are not limited to, conservative amino acid substitutions and modifications, for example, amidation of the carboxyl terminus, acetylation of the amino terminus, conjugation of the polypeptide to a physiologically inert carrier molecule, or sequence alterations in accordance with the serine esterase conserved sequences." The meaning of the term is therefore defined, however, it would require undue experimentation for one of skill in the art to make and use all peptides that may fall within the definition. Minor chemical derivatives that clearly do not affect the function of the peptide such as amidation are enabled. Additions, deletions and

substitutions, even those that "do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence" are not enabled.

The Wands factors have been detailed above. In the instant case, the amount of experimentation is large since, within the 308 permitted amino acids (since the derivative must be shorter than thrombin itself) there are 12 that make up the serine esterase conserved sequence and four that make up the receptor binding domain, leaving 292 positions available for substitution. With 20 natural amino acids that makes 292*20 = 5840 possible substitution mutants. Permitting one deletion tacks on 19*291= 5529 more peptides to test. This shortly adds up to a very large number of peptides to test for angiogenic activity. The amount of guidance presented is limited to the single physiologically functional equivalent having carboxy-terminal amidation. Working examples are presented, however, they show only TP508, not even an amidated version of TP508. The nature of the invention is a new use for known peptides; the state of the prior art is that these thrombin derivatives are known. The ordinary level of skill in this art is very high. The level of predictability of which of the many many peptides within the definition of the physiologically functional equivalent is zero. It is well known that even a single amino acid mutation can disrupt the function of a protein; hemoglobin is the classic example of that. Thus, the analysis leads to the inescapable conclusion of nonenablement.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

5. This is the first of two written description rejections.

Claims 1, 6-16, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As stated above, these claims read on a method using literally any peptide with angiogenic activity that has fewer amino acids than thrombin, or less than 308 amino acids. The only disclosure is those angiogenic peptides having at least 23 amino acids but not more than 307 amino acids comprising a polypeptide derivative of thrombin which has a thrombin receptor binding domain with a serine esterase conserved sequence. No structure-to-function relationship is disclosed other than the combination of the thrombin receptor binding domain and a serine esterase conserved sequence. Thus, it is clear that applicant was not in possession of the full range of peptides within the scope of these claims.

6. This is the second of two written description rejections.

Claims 1, 6, 9-19, 24, 27 and 28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant physiologically functional equivalents read on "molecules which differ from thrombin derivatives in particulars which do not affect the function of the thrombin receptor binding domain or the serine esterase conserved amino acid sequence." Applicant has disclosed only a carboxy-terminal amidated peptide; it is considered that peptides bearing minor chemical modifications like amidation are placed in the possession of the public by the disclosure of the non-amidated peptides. However, the myriad addition, deletion and substitution mutants that may fall within the broad definition of a physiologically functional equivalent have not been placed within the possession of the public. No structure-to-function relationship is disclosed for these addition, deletion and substitution mutants; in fact there seems to be no such relationship. Thus, it is clear that applicant was not in possession of the full range of peptides within the scope of these claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-10, 13, 14 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malinda et al. in view of Unger et al. and Carney et al. ('644).

Malinda et al. teach the exact method claimed in this application except that they use thymosin α1 as the angiogenic agent. Attention is directed to column 16, lines 5-36, especially lines 28-33 where it states, "For example, thymosin α1 peptide can be administered to prevent or treat tissue damage in cardiac tissue resulting from an incomplete or complete coronary occlusion by inducing angiogenesis and stimulating collateral circulation in the tissue affected by the occlusion." They discuss use of thymosin α1 to accelerate wound healing at column 2, lines 19-23, *inter alia*.

Unger et al. teach a method by which peptides may be made operable in vivo to promote new cardiac blood vessel growth in mature cardiac tissue, when such peptides have only been previously characterized or shown to promote the growth of blood vessels in vitro or in embryonic tissue at column 4, lines 6-12. They discuss particular peptides at column 5, line 40 *ff*.

Carney et al. ('644) teach the angiogenic thrombin derivative peptides used in the instant methods. At column 6, line 61 they discuss carboxy-terminal amides as within the definition of the physiologically functional equivalent.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the peptides of Carney et al. ('644) as angiogenic agents in the method of Malinda et al. with the expectation of beneficial results. Motivation is provided by Unger et al. who disclose other angiogenic agents other than thymosin α1, one of ordinary skill would therefore be led to expect that any angiogenic agent would

work to promote cardiac cell growth and revascularization in accordance with the teachings of Malinda et al. This expectation would apply to such common derivatives as carboxy-terminal amides, thus, claims 6-8 are included in this rejection.

9. Claims 11 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malinda et al. in view of Unger et al. and Carney et al. ('644) as applied to claims 1-10, 13, 14 and 28 above, and further in view of Thim et al.

The teachings of Malinda et al., Unger et al. and Carney et al. ('644) have been outlined above.

Thim et al. teach a peptide for pharmaceutical use in a sustained release formulation comprising the peptide in microcapsules made of lactic acid/glycolic acid copolymers, see column 10, lines 10-17.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to place the peptides of Carney et al. ('644) into sustained release microcapsules for administration according to the method of Malinda et al. with the expectation of attaining the well-known benefits of sustained release of medicine.

10. Claims 15, 16, 17 and 20-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malinda et al. in view of Unger et al. and Carney et al. ('644) as applied to claims 1-10, 13, 14 and 28 above, and further in view of Saadat et al.

The teachings of Malinda et al., Unger et al. and Carney et al. ('644) have been outlined above.

Saadat et al. teach stents coated with bioactive agent to stimulate revascularization and/or tissue growth, see column 4, line 63 – column 5, line 16. They name particular agents but state that other agents including peptides may be used as well.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to coat stents with the peptides of Carney et al. ('644) as the bioactive agent when practicing the method of Saadat et al. with the expectation of achieving the beneficial results taught by Carney et al. ('644). With specific regard to claims to inhibiting restenosis, Saadat et al. discuss stenosis at column 11, lines 31-40 and the action of the angiogenic agent. One of ordinary skill in the art would immediately realize that, since the reason for the use of the stent in the first place is to relieve stenosis then use of the angiogenic agent would by definition inhibit restenosis in the patient.

11. Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Malinda et al. in view of Unger et al., Carney et al. ('644) and Saadat et al., as applied to claims 12, 14 and 16 - 21 above, and further in view of Nakahara et al.

The teachings of Malinda et al., Unger et al., Carney et al. ('644) and Saadat et al. have been outlined above.

Nakahara et al. teach a pharmaceutical peptide administered directly into the lesion of a blood vessel via a drug delivery catheter or coated on the surface of a stent or balloon which is then administered to the lesion of a blood vessel or introducing the

peptide into the vein or artery as a bolus or continuously. They also disclose systemic administration of the peptide.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to coat the peptides of Carney et al. ('644) onto a balloon for administration with the expectation of achieving the benefits taught by Nakahara et al.

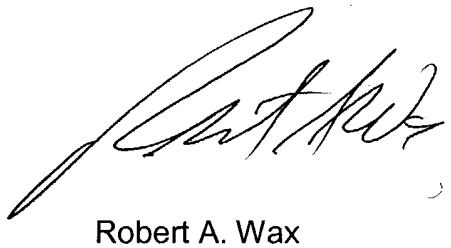
Conclusion

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday, between 9:00 AM and 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher S. F. Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Robert A. Wax
Primary Examiner
Art Unit 1653